REMARKS

Claims 1-42 are pending. Claims 37-42 have been withdrawn. Claims 1-36 are rejected.

CLAIM REJECTIONS-35 U.S.C. §102

Claims 1-5, 10-15, 20-22, and 27-31 were rejected under 35 U.S.C. §102 (a) as being anticipated by Alemany et al. The Examiner states:

> Alemany recites a method for nucleotide transfer and expression in recipient cells comprising introducing into the cells (which can be tumor cells) first and second replication incompetent adenoviral vectors (one of which is an E1 mutant and that the E1 coding reagent is under control of a heterologous promoter sequence) which are complementary in trans so that upon cotransformation viral replication is enabled.

PTO Paper 9 at 2-3.

Applicants have amended independent claims 1, 14, 20, and 31 to recite in part that "each vector is capable of sustained viral replication and capable of being produced independently of each other in separate trans-complementing packaging cell lines, thereby providing individual higher titer than vectors that are produced co-dependently on the same packaging cell line." A prior art patent, publication, or event is for the same "invention", as that word is used in §102, and therefore anticipating, if the prior art patent, publication, or event discloses each and every limitation found in the claims, either expressly or inherently. *Rockwell Intern. Corp. v. U.S.*, 147 F.3d 1358, 1363 (Fed. Cir. 1998). Each claim limitation must be found in a single prior art references. Applicants respectfully submit that Alemany's vector system is constructed such that the titer of the vector system purified from HepG2 cell is 50-fold lower than the titers that can be obtained from Applicants' vector system. Alemany et al discloses that they get vector yields 10 TU/cell, while each of Applicants' vectors can be produced independently in packaging cell lines to efficiencies of up to 500 TU/cell yielding titers of purified vector of up to about 10^{12} transducing unit/ml. This allows, for example, the injection of more viruses into a tumor. Therefore, Alemany does not disclose each limitation of Applicants' invention, therefore there is no anticipation.

Applicants would respectfully bring to the attention of the Examiner enclosed U.S. Patent 6,403,370, which Applicants request the Examiner to review submit into the record. Applicants believe this patent is duplicative of the cited Alemany reference.

Claims 1-3 and 13 were rejected under 35 U.S.C. 102 (b) as being anticipated by Salmons et al. The Examiner states:

> Salmons et al. *Human Gene Therapy*, 1993, Vol. 4, pp. 129-141, see whole article, particularly p.130, second to fourth paragraphs, Fig. 2 and Fig. 3, recites a method for nucleotide sequence transfer and expression in cells comprising introducing into cells a first and a second replication incompetent retroviral wherein said vectors are complimentary in trans so that upon cotransfection viral replication is enabled. Salmons et al. therefore teaches the claimed invention.

Id. at 4.

A prior art patent, publication, or event is for the same "invention", as that word is used in §102, and therefore anticipating, if the prior art patent, publication, or event discloses each and every limitation found in the claims, either expressly or inherently. *Rockwell Intern. Corp. v. U.S.*, 147 F.3d 1358, 1363 (Fed. Cir. 1998). Each claim limitation must be found in a single prior art references. Applicants respectfully submit that Salmons disclose a general overview of retroviral vectors for human gene therapy protocols. Salmons disclose old techniques of retroviral vector packaging which uses the concept of genetic transcomplementation and targeting. Additionally, Salmons discloses the packaging of retroviral vectors and cell lines engineered to have retroviral transcomplementation functions. The cell lines disclosed in Salmons are made of stable genomic integration of a defective retrovirus which encodes all transcomplementation functions necessary for virion production, but is devoid of all cis-acting sequences necessary for replication and packaging. Therefore, in a packaging cell line, as disclosed in Salmons, the transcomplementing vector does not replicate and is not packaged into virions. After transfection/transduction of a packaging cell line with a retroviral vector, the cell line packages this vector into virions. So, the final outcome is a supernatant containing only one type of vector. This is distinctly different from Applicants' invention because Applicants discloses and claims (see claim 1) at least two (2) transcomplementing vectors wherein **both** vectors have the cis-acting sequences necessary for replication and packaging signals, and both contribute to a formation of the virion, and both have mutations that prevent any of them to replicate independently from the other. Thus, the final outcome in Applicants' invention of the two vector transcomplementation system is a mixture of two vectors. This is inherently different from the system disclosed in Salmons. Additionally, Applicants respectfully submit that Salmons does not stand for the proposition the Examiner is exerting, particularly on page 130,

second to fourth paragraph, Fig. 2 and Fig. 3. Applicants failed to understand why the Examiner specifically pointed out this section as it does not even disclose transcomplementing viruses. Thus, Applicants respectfully submit that Salmons does not anticipate, expressly or inherently, and requests that this rejection be withdrawn.

Claims 1-5, 6-7, 13-17, 20-21, 23-24, 30-32, and 33-34 were rejected under 35 U.S.C 102(e) as being anticipated by Perricaudet et al. U.S. Application 2003/0096787. The Examiner states:

> Perricaudet et al. (U.S. 2003/0096787, published 5/22/03, priority to 1994, see whole document, particularly paragraphs 0029, 0034, 0038, 0055, 0148, 0169, 0175) recites a method for nucleotide transfer and expression in cells comprising introducing into the cells a first and a second replication incompetent adenoviral vector wherein one of the vectors can be a E1 and/or E3 and/or E4 mutant and wherein said vectors are complimentary in trans so that upon contransfection into cells viral replication is enabled. The first and second viral vectors comprise a nucleotide sequence which can encode an adenoviral product (i.e. E4, E3, etc.) the expression of which is desired in the cell.

Id. at 5-6.

A prior art patent, publication, or event is for the same "invention", as that word is used in §102, and therefore anticipating, if the prior art patent, publication, or event discloses each and every limitation found in the claims, either expressly or inherently. *Rockwell Intern. Corp. v. U.S.*, 147 F.3d 1358, 1363 (Fed. Cir. 1998). Each claim limitation must be found in a single prior art references. Applicants respectfully submit that Perricaudet et al. discloses in general, recombinant adenovirus as vectors for gene therapy. Perricaudet et al. discloses that the packaging of multiple defective adenoviral vectors (mutants in E1/E3/E4/L5) can be accomplished by cotransfection of DNA encoding the defective recombinant adenovirus helper transcomplimenting miniAd vector. Under the system of Perricaudet, viral replication of both vectors is <u>not</u> sustained. Unlike Applicants' invention (see claims 1, 14, 20, and 31), there is no <u>sustained</u> viral transcomplementation and replication as the transcomplementing helper virus is not a replication competent vector and the defective replication functions of the helper cannot be transcomplemented by the defective recombinant adenoviral vector. This results in the packaging of the defective recombinant vectors of Perricaudet to be restricted to only one cycle of infection. Perricaudet does not show this limitation, therefore does not anticipate.

Additionally, Perricaudet does not disclose the concomitant and simultaneous replication of both vectors as a means to increase gene transfer and cell lysis. Instead, Perricaudet discloses

how to package adenoviral vectors carrying mutations of multiple genes such as E1/E3/E4. Applicants respectfully request this rejection be withdrawn.

CLAIM REJECTIONS-35 U.S.C. 112, FIRST PARAGRAPH

Claims 8-9, 18-19, 25-26, and 35-36 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The Examiner states:

> Applicants claim methods of increasing nucleotide transfer and expression in recipient cells comprising using the recombinant adenovirus 1014 vector AVC2.TK vector. Applicants do not recite the generation of these vectors in a manner sufficient to enable the skilled artisan to reliably reproduce the exact claimed vectors. For example, Applicants merely recite that "1014 is a mutant with open reading frame 4 expressed." The prior art likewise does not provide the skilled artisan with the wherewithal to reliably reproduce the claimed vectors. Since the claimed vectors are essential for practicing the claimed invention, Applicants must deposit these vectors to satisfy the enablement requirement under 35 U.S.C. 112, first paragraph (See Attachment on Deposits of Biological Materials).

Id. at 6.

Applicants respectfully traverse this rejection. Applicants respectfully submit the specification is enabling as filed to allow one of ordinary skill in the art to generate the recombinant adenovirus 1014 vector and the AVC2.TK vector as required for practicing the invention. Applicants disclose on page 33, starting at line 23, that they employ two replication deficient adenoviral vectors. One is H5.DL104 wherein the Applicants cite Bridge et al., 1990. This reference, cited in the Information Disclosure Statement and enclosed herein for Examiner's convenience, discloses how to make the recombinant adenovirus 1014 vector (see Bridges et al. "Materials and Methods", page 795, column 1). Bridge discloses that the H5DL 1014 is identical to H5DL 1019 with some exceptions. However, provides disclosure sufficient to generate the 1014 vector. On page 34 of the specification, starting at line 20 and entitled "Adenoviral Vector", Applicants disclose the AVC2.null is identical to the AVC2.TK except for the absence of the hsv-tk transgene which was generated by the technique of Graham (Graham et al., 1997), which is also cited in the Information Disclosure Statement and described in the Applicants' specification (see spec. page 34, lines 21-34, to page 75, lines 1-8). Therefore, Applicant's specification recites the generation of these vectors in a manner that would enable a skilled artisan to reproduce the claimed vectors, therefore is enabling. Applicants respectfully request this rejection be withdrawn.

CLAIM REJECTIONS-35 U.S.C. 112, SECOND PARAGRAPH

Claims 3-9, 11-12, 28-29, and 32 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The Examiner states:

> Claim 3 is vague in that Applicants recite a vector selected from a group of viruses, not viral vectors. Redrafting the claim to recite a group consisting of retroviral vectors, adenoviral vectors, herpes viral vectors, etc. would be remedial.

Id. at 7.

Applicants have amended claim 3 according to Examiner's suggestion.

The Examiner states:

> Claim 4 is vague in that there is no antecedent basis for the term "said virus" in the claims from which claim 4 depends.

Id.

Applicants have amended claim 4 to recite "the method of claim 3 wherein said vectors are adenoviral vector", thereby providing proper antecedent basis.

The Examiner states:

> Claim 5 is vague in that there is no antecedent basis for the term "said first or second replication incompetent adenoviral vector".

Id.

Applicants have amended claim 5 to depend from new claim 43 by reciting "the method of claim 43 wherein said first vector is an E1 mutant".

The Examiner states:

> Claims 11-12 and 28-29 are vague in that they recite a sequence which encodes a tumor suppressor gene or a tumor suicide gene. The Examiner states a nucleotide sequence encodes a protein or polypeptide and not a gene. Redrafting the claims to recite a sequence which encodes a tumor suppressor protein or a tumor suicide gene product would be remedial.

Id.

Applicants have amended claim 11 to recite "the method of claim 1 wherein said sequence is a tumor suppressor gene" and claim 12 to recite "the method of claim 1 wherein said sequence is a tumor suicide gene", thereby making the claims clearer.

The Examiner states:

> Claim 32 is vague and the recitation of the term "E1-/E3 deletion mutant". It is unclear if Applicants are reciting a mutant with a deletion in E1 **and** E3?

Id.

Claim 32 has been amended to recite "the method of claim 46 wherein said first replication incompetent adenoviral vector is an E1 deletion mutant". Claim 34 has been amended to indicate that this vector can also be an E3 mutant in addition to mutant in E1, thereby making the claim clearer.

CONCLUSION

Please charge Deposit Account in the amount of number 26-0084 in the amount of $140.00 to cover the cost of the multiple dependent claims. It is believed that no other fees are due in connection with this amendment, however any deficiency or overpayment should be charged or credited to Deposit Account 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,

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